IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

HORIZON THERAPEUTICS, INC.,	§	
	§	
Plaintiff,	§	
	§	
v.	§	Case No. 2:14-cv-00384-JRG-RSP
	§	
PAR PHARMACEUTICAL, INC.,	§	
	§	
Defendant.	§	

MEMORANDUM OPINION AND ORDER

Defendant Par Pharmaceutical, Inc. filed an Abbreviated New Drug Application ("ANDA") seeking the FDA's approval to market a generic version of Plaintiff Horizon Therapeutics, Inc.'s drug Ravicti. Par's ANDA filing gave rise to this patent infringement dispute. On August 12, 2015, the Court held a hearing to determine the proper construction of nine disputed terms in two asserted patents: U.S. Patent No. 8,404,215 ("the '215 patent") and U.S. Patent No. 8,642,012 ("the '012 patent"). The Court, having considered the parties' claim construction briefing (Doc. Nos. 70, 74, 76) and arguments at the hearing, issues this Memorandum Opinion and Order construing the disputed terms.

I. BACKGROUND AND THE ASSERTED PATENTS

The '215 patent and the '012 patent describe methods for treating nitrogen retention disorders such as urea cycle disorders ("UCD") and hepatic encephalopathy ("HE"). ('215 patent col. 1, ll. 13–15.)[1,2] UCDs, for example, are caused by deficiencies in the enzymes or

[1] The '215 patent issued on March 26, 2013. The '215 patent was filed on March 9, 2012 and claims priority to provisional application no. 61/564,668, filed on November 29, 2011 and provisional application no. 61/542,100, filed on September 30, 2011.

[2] The '012 patent issued on February 4, 2014. The '012 patent was filed on January 7, 2009 and claims priority to provisional application no. 61/093,234, filed on August 29, 2008.

transporters necessary for synthesizing ammonia into urea. (’215 patent col. 1, ll. 17–19; Doc. No. 70-8 at 1606S-1608S.) Patients with UCDs suffer from numerous effects, some of which are described in the ’215 patent. (*See, e.g.*, ’215 patent col. 21, ll. 27–29; *see also* Doc. No. 70-8 at 1605S (“The main manifestation that is observed when blood ammonium levels increase is central nervous system dysfunction including stupor, convulsions, and coma.”).) When treating patients with UCDs the major objective is to control hyperammonemia. (Doc. No. 70-7 at 324.) That refers to avoiding “hyperammonemic crises, which are often defined in the art as transient ammonia values exceeding 100 µmol/L or 178 µg/mL accompanied by clinical signs and symptoms of hyperammonemia.” (’215 patent col. 4, ll. 42–45.)

The ’215 patent teaches that nitrogen retention disorders can be treated using nitrogen scavenging drugs that are well-known in the art. (’215 patent col. 1, ll. 50-56 (“Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled. . . are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate . . . or sodium benzoate.”).) An example of a nitrogen scavenging drug is sodium phenylbutyrate which belongs to a class of drugs known as phenylacetic acid (“PAA”) prodrugs. (’215 patent col. 1, ll. 59-60; *see also* Doc. No. 70-7 at 324.) Treating a patient with a PAA prodrug assists the patient with control of her blood ammonia levels. (’215 patent col. 4, ll. 39-41.)

According to the ’215 patent “there is a need in the art for improved methods for PAA prodrug dose determination and adjustment based on ammonia levels in subjects with nitrogen retention disorders such as [urea cycle disorders or hepatic encephalopathy].” (’215 patent col. 3, ll. 1-3.) For example, the ’215 patent claims this improved method:

> A method for adjusting the dosage of a nitrogen scavenging drug in a subject who has previously been administered an initial dosage of the nitrogen scavenging drug, comprising:
> a. measuring a fasting blood ammonia level for the subject;
> b. comparing the fasting blood ammonia level to the upper limit of normal for blood ammonia level; and
> c. administering an adjusted dosage of the nitrogen scavenging drug, wherein the adjusted dosage is greater than the initial dosage if the fasting blood ammonia level is greater than half the upper limit of normal for blood ammonia level.

('215 patent col. 24, ll. 28-39.)

The '012 patent also discloses methods that "provide[] a novel approach for determining and adjusting the schedule and dose of orally administered nitrogen scavenging drugs." ('012 patent col. 3, ll. 10-13.) For example, the '012 patent claims this novel approach:

> A method of administering a phenylacetic acid (PAA) prodrug selected from glyceryl tri-[4-phenylbutyrate] (HPN-100) and phenylbutyric acid (PBA) or a pharmaceutically acceptable salt of PBA to a patient having a [] urea cycle disorder comprising (a) administering a first dosage of the PAA prodrug; (b) determining urinary phenylacetyl glutamine (PAGN) excretion following administration of the first dosage of the PAA prodrug; (c) determining an effective dosage of the PAA prodrug based on the urinary PAGN excretion, wherein the effective dosage is based on a mean conversion of PAA prodrug to urinary PAGN of about 60%; and (d) administering the effective dosage to the patient.

('012 patent col. 42, ll. 42-53.)

II. PERSON OF ORDINARY SKILL

Horizon and Par generally agree that in the context of the '215 patent and the '012 patent a person of ordinary skill in the art is a physician or scientist with a M.D. or a Ph.D. This person of ordinary skill in the art would have training and experience in the diagnosis or treatment of inherited metabolic disorders such as urea cycle disorders and other nitrogen retention disorders. (Doc. No. 74 at 3.) The training should include at least post-graduate training and a certification in the fields of Clinical Genetics, Clinical Biochemical Genetics, or Medical Biochemical

Genetics by the American Board of Medical Genetics and Genomics. (Doc. No. 74 at 3; Doc. No. 70-1 ¶ 24.)

III. APPLICABLE LAW

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). To determine the meaning of the claims, courts start by considering the intrinsic evidence. *Id.* at 1313; *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 861 (Fed. Cir. 2004); *Bell Atl. Network Servs., Inc. v. Covad Commc'ns Group, Inc.*, 262 F.3d 2158, 1267 (Fed. Cir. 2001). The intrinsic evidence includes the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1314; *C.R. Bard, Inc.*, 388 F.3d at 861. The general rule—subject to certain specific exceptions discussed below—is that each claim term is construed according to its ordinary and accustomed meaning as understood by one of ordinary skill in the art at the time of the invention in the context of the patent. *Phillips*, 415 F.3d at 1312–13; *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1368 (Fed. Cir. 2003); *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002) ("Generally speaking, we indulge a 'heavy presumption' that a claim term carries its ordinary and customary meaning.")

The claims themselves provide substantial guidance in determining the ordinary meaning of claim terms. *Phillips*, 415 F.3d at 1314. "The claim construction inquiry . . . begins and ends in all cases with the actual words of the claim." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). First, a term's context in the asserted claim can be instructive. *Id*. Other asserted or unasserted claims can also aid in determining the claim's meaning, because claim terms are typically used consistently throughout the patent. *Phillips*, 415

F.3d at 1314. Differences among the claim terms can also assist in understanding a term's meaning. *Id*. For example, when a dependent claim adds a limitation to an independent claim, it is presumed that the independent claim does not include the limitation. *Id*. at 1314–15.

"[C]laims 'must be read in view of the specification, of which they are a part.'" *Id*. (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc)). "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Id*. (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). But, "'[a]lthough the specification may aid the court in interpreting the meaning of disputed claim language, particular embodiments and examples appearing in the specification will not generally be read into the claims.'" *Comark Commc'ns, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187 (Fed. Cir. 1998) (quoting *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988)); *see also Phillips*, 415 F.3d at 1323. "[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment—into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited." *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004).

The prosecution history is another tool that supplies proper context for claim construction because, like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent. *Id.* at 1317. However, "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.* at 1318; *see also Athletic Alternatives, Inc. v. Prince Mfg.*, 73 F.3d

1573, 1580 (Fed. Cir. 1996) (ambiguous prosecution history may be "unhelpful as an interpretive resource").

Although extrinsic evidence can also be useful, it is "'less significant than the intrinsic record in determining the legally operative meaning of claim language.'" *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc.*, 388 F.3d at 862). Technical dictionaries and treatises may help a court understand the underlying technology and the manner in which one skilled in the art might use claim terms, but technical dictionaries and treatises may provide definitions that are too broad or may not be indicative of how the term is used in the patent. *Id*. at 1318. Similarly, expert testimony may aid a court in understanding the underlying technology and determining the particular meaning of a term in the pertinent field, but an expert's conclusory, unsupported assertions as to a term's definition are entirely unhelpful to a court. *Id*. Generally, extrinsic evidence is "less reliable than the patent and its prosecution history in determining how to read claim terms." *Id*.

A. Departing from the Ordinary Meaning

There are "only two exceptions to [the] general rule"[3] that claim terms are construed according to their plain and ordinary meaning: "1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee disavows the full scope of the claim term either in the specification or during prosecution." *Golden Bridge Tech., Inc. v. Apple Inc.*, 758 F.3d 1362, 1365 (Fed. Cir. 2014) (quoting *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012)); *see also GE Lighting Solutions, LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014) ("[T]he specification and prosecution history only compel departure

[3] Some cases have characterized other principles of claim construction as "exceptions" to the general rule, such as the statutory requirement that a means-plus-function term is construed to cover the corresponding structure disclosed in the specification. *See, e.g.*, *CCS Fitness*, 288 F.3d at 1367.

from the plain meaning in two instances: lexicography and disavowal."). The standards for finding lexicography or disavowal are "exacting." *Id.*

To act as his own lexicographer, the patentee must "clearly set forth a definition of the disputed claim term," and "clearly express an intent to define the term." *Id.* (quoting *Thorner*, 669 F.3d at 1365); *see also Renishaw*, 158 F.3d at 1249. The patentee's lexicography must appear "with reasonable clarity, deliberateness, and precision." *Id.*

To disavow or disclaim the full scope of a claim term, the patentee's statements in the specification or prosecution history must amount to a "clear and unmistakable" surrender. *Cordis Corp. v. Boston Sci. Corp.*, 561 F.3d 1319, 1329 (Fed. Cir. 2009); *see also Thorner*, 669 F.3d at 1366 ("The patentee may demonstrate intent to deviate from the ordinary and accustomed meaning of a claim term by including in the specification expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.") "Where an applicant's statements are amenable to multiple reasonable interpretations, they cannot be deemed clear and unmistakable." *3M Innovative Props. Co. v. Tredegar Corp.*, 725 F.3d 1315, 1326 (Fed. Cir. 2013).

B. Claim Indefiniteness

Patent claims must particularly point out and distinctly claim the subject matter regarded as the invention. 35 U.S.C. § 112, ¶ 2. "[I]ndefiniteness is a question of law and in effect part of claim construction." *ePlus, Inc. v. Lawson Software, Inc.*, 700 F.3d 509, 517 (Fed. Cir. 2012). A party challenging the definiteness of a claim must show it is invalid by clear and convincing evidence. *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1345 (Fed. Cir. 2007).

The definiteness standard of 35 U.S.C. § 112, ¶ 2 requires that:

> [A] patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty. The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable. The standard we adopt accords

> with opinions of this Court stating that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter."

Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2129–30 (2014) (internal citations omitted).

IV. CONSTRUCTION OF AGREED TERMS

The parties resolved their disputes on three terms: "urea cycle disorder" which appears in the '215 patent and the '012 patent (Doc. No. 80-2 at B-2), "first dosage" which appears in the '012 patent (Doc. No. 80-2 at B-1), and "urinary PAGN of 60-75%" which appears in the '215 patent. (Doc. No. 112 at 73:17–20 ("[O]n the '012 patent, those terms are not agreed; is that – is that right? That's right, Your Honor.").) The Court adopts the parties' constructions and finds that "urea cycle disorder" means "**an inherited deficiency of an enzyme or transporter necessary for the synthesis of urea from ammonia, including enzymes involved in the urea cycles**"; "first dosage" should be given its **plain and ordinary meaning**; and "urinary PAGN of 60-75%" should be given is **plain and ordinary meaning**.

V. CONSTRUCTION OF DISPUTED TERMS

A. The "Upper Limit of Normal" Terms

Disputed Terms	Horizon's Proposed Construction	Par's Proposed Construction
"upper limit of normal" '215 patent, claims 1–3, 10	"the highest level in the range of normal values"	indefinite
"determining an upper limit of normal" '215 patent, claim 9	"determining the highest level in the range of normal values"	indefinite
"half the upper limit of normal" '215 patent, claims 1–3	"half the highest level in the range of normal values"	indefinite

The parties do not dispute that the "upper limit of normal" is the upper limit in a range of values. (*See* Doc. No. 74 at 16 ("The range for blood ammonia level (a high and low value) is similar to a range of cholesterol levels shown on a routine check-up from a doctor.").) However, the parties dispute whether the term "upper limit of normal" is indefinite because multiple ranges of values can constitute a "normal" range. (*See* Doc. No. 74 at 16 ("Because each lab produces a different 'upper limit or normal,' the '215 patent does not 'conclude with . . . claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.'").)

Horizon's Position

Horizon claims that the '215 patent provides an "express definition" for "upper limit of normal" which is that "[t]he [upper limit of normal] for blood ammonia typically represents the highest level in the range of normal values." ('215 patent col. 12, ll. 18–19.) As support for its claim Horizon points to several places in the specification where the patentee describes the "upper limit of normal" as "a normal range" ('215 patent col. 4, ll. 39–43) or "in the range of" certain values ('215 patent col. 12, ll. 47–56).

Horizon also claims that its proposed definition is "consistent with the general understanding of a person of skill in the art at the time of invention." (Doc. No. 70 at 8.) It cites Dr. Gregory M. Enns who says that "when measurements of blood ammonia levels are taken for different individuals, the measurement will result in a range of values" (Doc. No. 70-1 ¶ 44) but even when the range is variable, a person of ordinary skill in the art "would understand that 'upper limit of normal' refers to the highest level in the range of normal values" (Doc. No. 70 at 9 (citing Doc. No. 70-1 ¶¶ 44–45, 53–54)).

Horizon disputes Par's assertion that "upper limit of normal" should be found indefinite. Horizon claims that "a person of ordinary skill in the art would understand how to use the range of normal blood ammonia values in a clinical setting" (Doc. No. 70 at 8 (citing Doc. No. 70-1 ¶¶ 44-47, 52-54)) "because laboratories that measure blood ammonia levels provide the laboratories' range of normal values with the test results for a patient" (Doc. No. 70 at 9 (citing Doc. No. 70-1 ¶ 54)). Furthermore, Horizon claims "the FDA-approved Ravicti labeling itself uses the term 'upper limit or normal,' specifically instructing treating physicians to adjust the nitrogen scavenging drug dosage to produce a 'fasting ammonia level that is less than *half the upper limit of normal* according to age.'" (Doc. No. 70 at 11.)

Par's Position

Par contends that the '215 patent does not expressly define the "upper limit of normal." (Doc. No. 74 at 15.) Par asserts that the "upper limit of normal" is indefinite since "an 'upper limit of normal' for a fasting blood ammonia level can be measured or determined lots of different ways." (Doc. No. 74 at 11.) Par points to an entire column of the '215 patent "devoted to describing diverse possible meanings of [upper limit of normal]." (Doc. No. 74 at 13.)

The column of the '215 patent cited by Par states that the "upper limit of normal" encompasses a "range of normal values" depending on "a variety of factors such as the assay method, types of re[a]gents, standard reference samples used, and specifications and calibration of equipment used to form the measurement." (Doc. No. 74 at 13 (quoting '215 patent col. 12, ll. 18–56).) It also states that the "upper limit of normal" can be determined based on a specific individual, a specific patient type, a specific laboratory range, or a range of individual values. (Doc. No. 74 at 13.) In addition, Par asserts that "Dr. Enns' deposition testimony explains why

these ranges do not render the claims definite." Dr. Enns' admits that the range of "normal" at least varies from laboratory to laboratory. (Doc. No. 74 at 16.)

Finally, Par asserts that this case is analogous to at least three cases where the Federal Circuit has found claims indefinite: (1) *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335 (Fed. Cir. 2015) "in which the Federal Circuit held that Teva's claims were indefinite because the term 'molecular weight' could be measured in at least three different ways" (Doc. No. 74 at 13); (2) *Honeywell International, Inc. v. ITC*, 341 F.3d 1332 (Fed. Cir. 2003) where "the Federal Circuit affirmed the International Trade Commission and held invalid certain claims that recited a 'melting point elevation' limitation because there were four different methods to measure the melting point elevation" (Doc. No. 74 at 14); and (3) *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d 1244 (Fed. Cir. 2008) because in both the claims in *Halliburton* and the claims in this case the claims "require[] the person of ordinary skill to 'make a separate infringement determination for ever set of circumstances'"(Doc. No. 74 at 17 (quoting *Halliburton*, 514 F.3d at 1249)).

Analysis

The Court finds that for five reasons, the term "upper limit of normal" is not indefinite and should be construed to have its **plain and ordinary meaning**. First, the claims of '215 patent show, by implication, that when practicing the method of the claims, a person of ordinary skill in the art would recognize, with "reasonable certainty," that the "upper limit of normal" is a number that is obtainable from a preexisting source. The claims do not describe how a person of ordinary skill in the art would determine the "upper limit or normal," but nevertheless, the claims recite that the "upper limit of normal" can readily be obtained and "compared" with a subject's

"fasting blood ammonia level" in practicing the method of the claims. (*See, e.g.*, '215 patent col. 24, ll. 33–34, 43–44, 52–54.)

Second, the specification teaches that the "upper limit of normal" can be obtained from a preexisting source. It states that "one skilled in the art will appreciate that interpretation of average daily ammonia . . . must be made relative to the reference range of normal values at the laboratory in which the ammonia was measured." ('215 patent col 12, ll. 38–43.) The specification further states that the inherent variations between laboratories "emphasiz[es] the importance of interpreting the subject's ammonia levels relative to the 'upper limit of normal' at the laboratory in which the measurement was performed." ('215 patent col 12, ll. 44–48.) The consistent use of the phrase "at the laboratory" teaches a person of ordinary skill in the art that the "upper limit of normal" is part of a range of values that can be readily obtained from a source such as a "laboratory." ('215 patent col. 20, ll. 16–18 ("This fasting blood ammonia level is compared to the [upper limit of normal] for blood ammonia for the laboratory performing the blood draw."); Doc. No. 74-3 at 6 ("Scharschmidt states at paragraph 0084 that 'In certain clinical tests described herein the upper limit of normal for the subjects was between 26 and 35 μmol/L.' This represents a fairly standard range for the upper limit of normal in a nitrogen retention disorder population, which varies somewhat from laboratory to laboratory.").)

Indeed, the specification discloses that the inventors, on several occasions, obtained the "upper limit of normal" from a laboratory for their studies. In one study, the inventors obtained "ammonia values" "from different hospital laboratories with different normal ranges." ('215 patent col. 15, ll. 34–35.) The inventors then "normalized" these "ammonia values" "to a standard laboratory range of 9–35 μmol/L" ('215 patent col. 15, ll. 35–36) to "take into account the differences in normal ranges at different laboratories" ('215 col. 16, ll. 28–30; *see also* '215

col. 19, ll. 28–30 (“This fasting blood ammonia level is compared to the [upper limit of normal] for blood ammonia in the laboratory performing the blood draw, which is 35 µmol/L.”)).

Third, that different laboratories or populations can generate different “upper limits of normal” does not render the term indefinite. The specification discloses the factors a person of ordinary skill in the art would consider when determining if a particular “upper limit of normal” is useful for practicing the method of the claims. The specification teaches that the person of ordinary skill in the art would consider if the “upper limit of normal” was determined: “for a subject individually,” “based on measurements obtained across a range of subjects,” using “a standard reference value disclosed in the art, such as a mean [upper limit of normal] developed across a particular subset of subjects,” or using “a standard reference value utilized by the same entity that measures the fasting blood ammonia level.” (’215 patent col. 12, ll. 23–38); *see, e.g.*, *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 348 F.3d 1373, 1383–84 (Fed. Cir. 2003) (“Our predecessor court has stated that ‘effective amount’ is a common and generally acceptable term for pharmaceutical claims and is not ambiguous or indefinite, provided that a person of ordinary skill in the art could determine the specific amounts without undue experimentation.”). The specification further teaches that a person of ordinary skill in the art would consider the inherent differences in laboratory convention and instrumentation when determining an “upper limit of normal.” (*See* ’215 patent col. 12, ll. 18–23 (“The ULN . . . may be influenced by a variety of factors such as the assay method, types of re[a]gents, standard reference samples used, and specifications and calibration of equipment used to perform the measurement.”).)

In sum, the intrinsic evidence shows that a person of ordinary skill in the art would be able to determine with “reasonable certainty” that the “upper limit of normal” was a preexisting number or range of numbers readily obtainable from a source such as a “laboratory.”

Furthermore, the intrinsic evidence shows that a person of ordinary skill in the art would recognize if a particular "upper limit or normal" was suitable for practicing the method of the claims.

Fourth, this interpretation of the "upper limit of normal" is consistent with the extrinsic evidence. The FDA label for Ravicti states that a physician treating a patient should "[a]djust the Ravicti dosage to produce a fasting plasma ammonia level that is less than half the upper limit of normal (ULN) according to age." (Doc. No. 70-10 at 3.) Likewise, a reference book published ten years before the filing date of the '215 patent teaches: "If the plasma ammonium level is greater than three times the upper limit of normal, all protein intake should be discontinued and adequate calories given either intravenously or enterally, if tolerated." (Doc. No. 70-12 at 836; *see also* Doc. No. 70-5 at 224 ("Blood ammonia values among all patients varied widely . . . . (upper limit of normal ranged from 26–35 μmol/L at the four sites) . . . .").)

Finally, Federal Circuit precedent does not require the Court to find that the "upper limit of normal" is indefinite. The '215 patent does not claim a product-by-process where the measurement of the "upper limit or normal" is a critical step to determining the structure or composition of the final product. *See Teva*, 789 F.3d at 1341 ("The parties agree that 'molecular weight' could refer to *M*p, *M*w, or *M*n. And they agree that each of these measures is calculated in a different way and would typically yield a different result for a given polymer sample."); *Honeywell*, 341 F.3d at 1332 ("Because the sample preparation method is critical in determining MPE, processes utilizing different sample preparation methods will produce different yarns."). Furthermore, '215 patent does not claim a functional improvement over the prior art but fail to describe the degree of improvement that the invention confers. *Halliburton*, 514 F.3d at 2153

("Halliburton's failure to distinguish the fragileness of the drilling fluids of the invention from the close prior art (the 12.1 SF fluid that exhibited the L-shaped curve behavior) is fatal.").

Because the term "upper limit of normal" is not indefinite, the Court adopts the plain and ordinary meaning of the term. The patentee did not expressly define "upper limit of normal," and the specification shows that the "upper limit of normal" can be at least a single number or range of numbers. ('215 patent col. 12, ll. 18–19 ("The [upper limit of normal] for blood ammonia typically represents the highest level in the range of normal values."); '215 patent col. 12, ll. 48–52 ("In certain of these embodiments, the [upper limit of normal] for blood ammonia may be in the range of 32–38 µmol/L or 34–36 µmol/L, and in certain of these embodiments the [upper limit of normal] for blood ammonia is 35 µmol/L.").)

B. The "Dosage" Terms

Disputed Terms	Horizon's Proposed Construction	Par's Proposed Construction
"initial dosage" '215 patent, claims 1, 3	"first dosage"	"starting dosage"
"adjusted dosage" '215 patent, claims 1, 3	"second dosage"	"a different dose than the initial dose"

The parties agree that "initial dosage" means the dosage that immediately precedes the "adjusted dosage." (*See* Doc. No. 112 at 67:3–4; 67:16–68:1 ("Your Honor, with regard to initial dosage, I think we are completely with your instruction, as well . . . . Our resistance to Plaintiff's construction of initial as first was our objection of an attempt by [Horizon] to basically suggest that initial and adjusted are two consecutive doses . . . . So we – we're fine with the Court's construction.").) The parties further agree that "initial dosage" does not mean the first dose that a patient has ever received. (*See* Doc. No. 112 at 67:17–19 ("I don't think we ever intended that

initial dosage meant the first dosage that a patient ever receives in their life.").) The parties dispute whether the "adjusted dosage" had to be a different "dosage" than the "initial dosage."

Horizon's Position

Horizon asserts that the specification clearly indicates that the "dosage administration process is iterative." (Doc. No. 70 at 13.) This, according to Horizon, means that the "process is repeated until a fasting blood ammonia level is reached that is less than or equal to half the [upper limit of normal]." (Doc. No. 70 at 13.) Horizon states that because the purpose of the invention is to achieve these results, Par's proposal that the "adjusted dosage" be construed to be a "different dosage than the initial dosage" (Doc. No. 74 at 6 n.3) is inconsistent with the specification. Horizon points to examples in the specification which "explicitly state[] that '[i]n certain embodiments, the effective dosage may be the same as or different than the initial dosage.'" (Doc. No. 70 at 15.)

Par's Position

Par responds by stating that the "common sense" meaning of "adjust" requires a person doing the "adjusting" to make a "change" from the preexisting state. (Doc. No. 74 at 7.) Because the patentee changed the language of the claims from "determined" to "adjusted" during prosecution, Par argues that the patentee intended the allowed claims to cover only circumstances in which the "adjusted dosage" was different from the "initial dosage." (Doc. No. 74 at 7.) Par finally points out that Horizon cites portions of the specification that do "not even mention the term 'adjusted dosage.'" (Doc. No. 74 at 8.)

Analysis

The Court finds, in accordance with the parties agreement, that the term "initial dosage" means "**a first dosage**." The Court finds that the term "adjusted dosage" has its **plain and**

ordinary meaning. The patentee used the word "adjusted" in claims 1 and 3 of the '215 patent. The word "adjusted" has a plain and ordinary meaning that requires something to be changed or altered in order for the thing to be "adjusted." Claims 1 and 3 provide examples of "adjusted dosages" in which the "adjusted dosages" are different from the "initial dosages" because they are "greater than the initial dosages." ('215 patent col. 24, ll. 35–39, 54–57.)

The specification discloses other examples of "adjusted dosages" that are different from the initial dosage. For example, the specification states that "[i]n certain embodiments, the effective dosage of nitrogen scavenging drug is determined by adjusting (e.g. increasing) a dosage to achieve a fasting blood ammonia level for a subject that is less than or equal to half the [upper limit of normal] for blood ammonia." ('215 patent col 6, ll. 21–25.)

The specification also shows that the patentee distinguished between "adjusted" and non-"adjusted" dosages because "[i]f the fasting blood ammonia level has a value that is greater than half the [upper limit of normal], subsequent maintenance dosages of the nitrogen scavenging drug are adjusted to be greater than the initial dosage." ('215 patent col. 7, ll. 32–36.) This teaches that a "maintenance dosage" can be either "adjusted" or non-"adjusted" and that an "adjusted dosage" is different from a non-"adjusted dosage." The claims of the '215 patent use the word "adjusted," and the Court expressly rejects Horizon's argument that an "adjusted dosage" and an "initial dosage" can be the same dosage.

C. "Normal Average Daily Ammonia Level"

Disputed Terms	Horizon's Proposed Construction	Par's Proposed Construction
"normal average daily ammonia level" '215 patent, claim 8	plain and ordinary meaning	indefinite

Parties' Positions

Horizon argues that "normal average daily ammonia level" is not indefinite because "[a]s explained above, there is a range of normal values for blood ammonia levels, recognized in both the specification, the literature, and by skilled artisans." (Doc. No. 70 at 10.) Par responds that the term "normal average daily ammonia level" "suffers the same ambiguity and vagueness as 'upper limit of normal.'" (Doc. No. 74 at 18.) Par asserts that the term "could mean any of the following: an average blood ammonia level for a healthy patient; an average blood ammonia level for a range of unspecified subjects with UCD; an average blood ammonia level determined by a particular laboratory; a specific numerical blood ammonia value measured in μmol/L." (Doc. No. 74 at 18.) Because a "normal average daily ammonia level" can be determined from any of these subpopulations, Par concludes the term does not inform a person of ordinary skill in the art with "reasonable certainty" about the scope of the claim. (Doc. No. 74 at 18.)

Analysis

The Court finds that this term means "**an average daily ammonia level within the normal range**." The specification defines "average daily ammonia." It states that "in certain embodiments, the average daily ammonia is the average amount of ammonia an individual may experience during the day, if serial blood sampling were performed for ammonia measurements." ('215 patent col. 12, ll. 57–60 (emphasis added).) The specification further states that the "average daily ammonia" can be calculated "as the area under the curve for 24-hr ammonia (ammonia $AUC_{0\text{-}24hr}$) obtained from adequate and well-spaced samples over 24 hours. This ammonia $AUC_{0\text{-}24hr}$ can be further normalized for the entire actual period of sampling, i.e., ammonia $AUC_{0\text{-}24hr}$ is divided by the sampling period (e.g. 24 hours)." ('215 patent col 13, ll. 5–11) (emphasis added). "For example, if an AUC of 1440 μmol*hr/ml is calculated using the

trapezoidal rule based on 8–11 ammonia values obtained over 24 hours, then the average daily ammonia value or time-normalized $AUC_{0\text{-}24hr}$ would be equal to 1440 μmol*hr/ml divided by the sampling time of 24 hr, or 60 μmol/L." ('215 patent col. 13, ll. 11–16.) The specification teaches that other methods of calculating the "average daily ammonia" will also suffice. ('215 patent col. 5, ll. 9–15 ("It was found that fasting ammonia correlates strongly with daily ammonia exposure, assessed as a 24 hour area under the curve for ammonia, daily average, or maximal daily concentration, and that a target fasting value which does not exceed half of the [upper limit of normal] is a clinically useful and practical predictor of ammonia values over 24 hours.").)

As with the "upper limit of normal" the specification uses "normal" to denote a range of values that a person of ordinary skill in the art performing the method of the claims could obtain from a preexisting source such as a laboratory. (*See, e.g.*, '215 patent col. 15, ll. 34–36 ("Ammonia values obtained from different hospital laboratories with different normal ranges were normalized to a standard laboratory range of 9–35 μmol/L.").) A "normal average daily ammonia level" equals an "ammonia" level that is within the "normal" range. In the context of "average daily ammonia," the specification discloses at least one example of that range. ('215 col. 13, ll. 16–19 ("If the normal reference range at the laboratory which performed the ammonia analysis was 10-35 μmol/L, then the average daily ammonia value for this subject would be approximately 1.71 times the [upper limit of normal] of 35 μmol/L.").)

D. "Treating"

Disputed Terms	Horizon's Proposed Construction	Par's Proposed Construction
"treating" '215 patent, claim 3	plain and ordinary meaning	"decreasing the blood nitrogen and/or ammonia level"

Horizon's Position

Horizon asserts that "treating" has a well-understood plain and ordinary meaning, and that meaning is reflected in the steps of claim 3 of the '215 patent. (Doc. No. 70 at 16.) Horizon also asserts that the specification discloses the purpose of the invention which is to control blood ammonia level by keeping it within a range. (Doc. No. 70 at 17.) According to Horizon, the specification does not require a physician to continue "decreasing the blood nitrogen and/or ammonia level" of a patient if the patient's "blood nitrogen and/or ammonia level" is already under control. (Doc. No. 70 at 17.)

Par's Position

Par responds that Horizon's construction of "treating" "strips [] treatment from the word" (Doc. No. 74 at 10) because the claims state that "treating" occurs when nitrogen scavenging drugs are administered, and by nature, nitrogen scavenging drugs decrease "blood nitrogen and/or ammonia levels" (Doc. No. 74 at 9, 10 n.5). Par argues that Horizon's proposed construction renders the word "administering" superfluous because Horizon's proposed construction equates "treating" and "administering." (Doc. No. 74 at 10.) Par concludes by arguing that "treating" should be distinct from "attempting to treat." (Doc. No. 74 at 11.)

Analysis

The Court finds that the term "treating" has its **plain and ordinary meaning**. The ordinary meaning of treating does not include an efficacy requirement. It requires a person of ordinary skill in the art "treating" a patient to attempt to assist the patient. Furthermore, "treating" appears only in the preamble of claim 3 of the '215 patent which states that claim 3 is "[a] method of treating a subject with a nitrogen retention disorder who has previously been administered an initial dosage of a nitrogen scavenging drug." ('215 patent col. 24, ll. 48–50.)

"Treating" according to claim 3 requires a person practicing the method of claim 3 to "measure[]" the patient's blood ammonia level, "compar[e]" the patient's blood ammonia level to an "upper limit of normal," and "administer[]" a nitrogen scavenging drug if the patient's blood ammonia level is "greater than half the upper limit of normal." ('215 patent col. 24, ll. 40–47.) Based on the language of the claims, the Court rejects Par's proposed construction of "treating" as "decreasing the blood nitrogen and/or ammonia level" of a patient. (Doc. No. 74 at 9.) Claim 3 expressly states that "treating" requires only the three listed steps to be performed on a "subject." Claim 3 does not require those steps to actually "decrease" the "subject's" "blood nitrogen and/or ammonia level."

Indeed, the specification discloses "methods of treating" where the patient's "blood nitrogen and/or ammonia level" is not decreased. ('215 patent col. 5, ll. 60–62.) The specification teaches that "[i]f the fasting blood ammonia level has a value that is greater than half the [upper limit of normal], the subject is administered a maintenance dosage that is greater than the initial dosage of the nitrogen scavenging drug. If the fasting blood ammonia level has a value that is less than or equal to half the [upper limit of normal], the subject is administered the initial dosage or a lower dosage." ('215 patent col. 8, l. 65–col. 9, l. 5.) The specification shows that "treating" a patient does not mean the patient's "blood nitrogen and/or ammonia level" must be "decreased." Administering a second dosage that is the same as the "initial dose" would not "decrease" the patient's "blood nitrogen and/or ammonia level" but would maintain the patient's "blood nitrogen and/or ammonia" at the same level.

E. "Normal Plasma Ammonia Level"

Disputed Terms	Horizon's Proposed Construction	Par's Proposed Construction
"normal plasma ammonia level" '012 patent, claim 12	plain and ordinary meaning	indefinite

Parties' Positions

Horizon states that a person of ordinary skill in the art would understand that measured blood ammonia levels can vary between individual patients, and that person would also understand that blood ammonia levels can fall within a range that is considered normal. (Doc. No. 70 at 23.) Horizon contends that this term is not indefinite because a person of ordinary skill in the art would know that a "normal plasma ammonia level' should be considered "by viewing the measured plasma ammonia values in light of what is considered normal for a given laboratory." (Doc. No. 70 at 24.) Par argues that "the parties' disagreement . . . over 'normal plasma ammonia level' in the '012 patent centers around the word "normal." (Doc. No. 74 at 22.) Par contends for the same reasons that any term with the word "normal" should be found indefinite. (Doc. No. 74 at 22.)

Analysis

The Court finds that the term "normal plasma ammonia level" is not indefinite and should be construed to mean "**plasma levels of ammonia that are at or below a level considered normal for the subject**." The '012 patent uses the term "normal plasma ammonia level" in claim 12 which recites: "The method of claim 8, wherein administration of the effective dosage of PAA prodrug produces a normal plasma ammonia level in the patent." ('012 patent col. 42, ll. 60–62.) The '012 patent defines the term "normal plasma ammonia level." It states: "As used

herein, plasma levels of ammonia are acceptable when they are at or below a level considered normal for the subject, and commonly this would mean plasma ammonia level is below about 40 µmol/L." ('012 patent col. 20, ll. 31–34; *see* '012 patent, at figs.5, 11, 12.)

VI. CONCLUSION

The Court adopts the above constructions set forth in this opinion for the disputed terms of U.S. Patent No. 8,404,215 and U.S. Patent No. 8,642,012. The parties are **ORDERED** that they may not refer, directly or indirectly, to each other's claim construction positions in the presence of the jury. Likewise, the parties are **ORDERED** to refrain from mentioning any portion of this opinion, other than the actual definitions adopted by the Court, in the presence of the jury.

SIGNED this 20th day of October, 2015.

ROY S. PAYNE
UNITED STATES MAGISTRATE JUDGE